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# Treatment with intravenous immunoglobulin increases the level of small EVs in plasma of pregnant women with Recurrent Pregnancy Loss

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## Introduction

Recurrent Pregnancy Loss (RPL) is the cause of childlessness in 2-5% of reproducing couples. Immunological mechanisms have been proposed as an etiology in some cases of RPL. Various forms of immunotherapy have been attempted in individuals thought to have an immunologic mechanism associated with RPL.

Intravenous immunoglobulin (Ivlg) has been tested in a placebo-controlled trial of women with RPL. In a blinded setup, some of the women were given treatment with intravenous immunoglobulin and the rest were given placebo (human albumin). Venous peripheral blood (EDTA) was obtained from the women at several time points during their pregnancy.

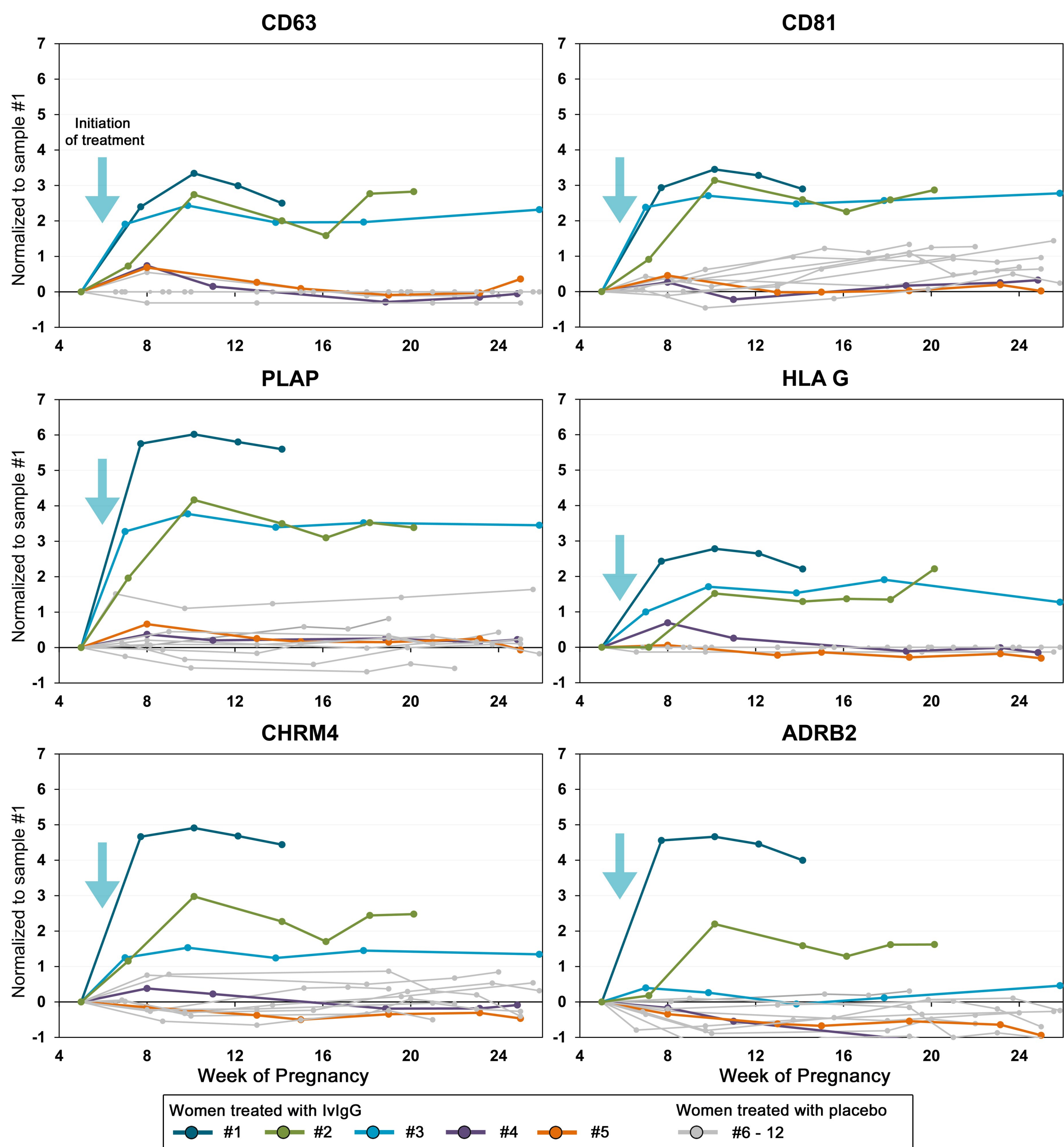
## Development over Time

The first of the sequential samples (obtained before the first infusion in pregnancy week 5) from each woman were used as reference point to which the rest of the samples were normalized in order to detect the change over time.

Already at the second sampling point (after 2-3 weeks) the level of small EVs (sEVs) carrying markers of interest increased massively (2-6 fold) in 3 of the 5 women treated with Ivlg. After 4-6 weeks, this increase stops and remains stable during the rest of the pregnancy.

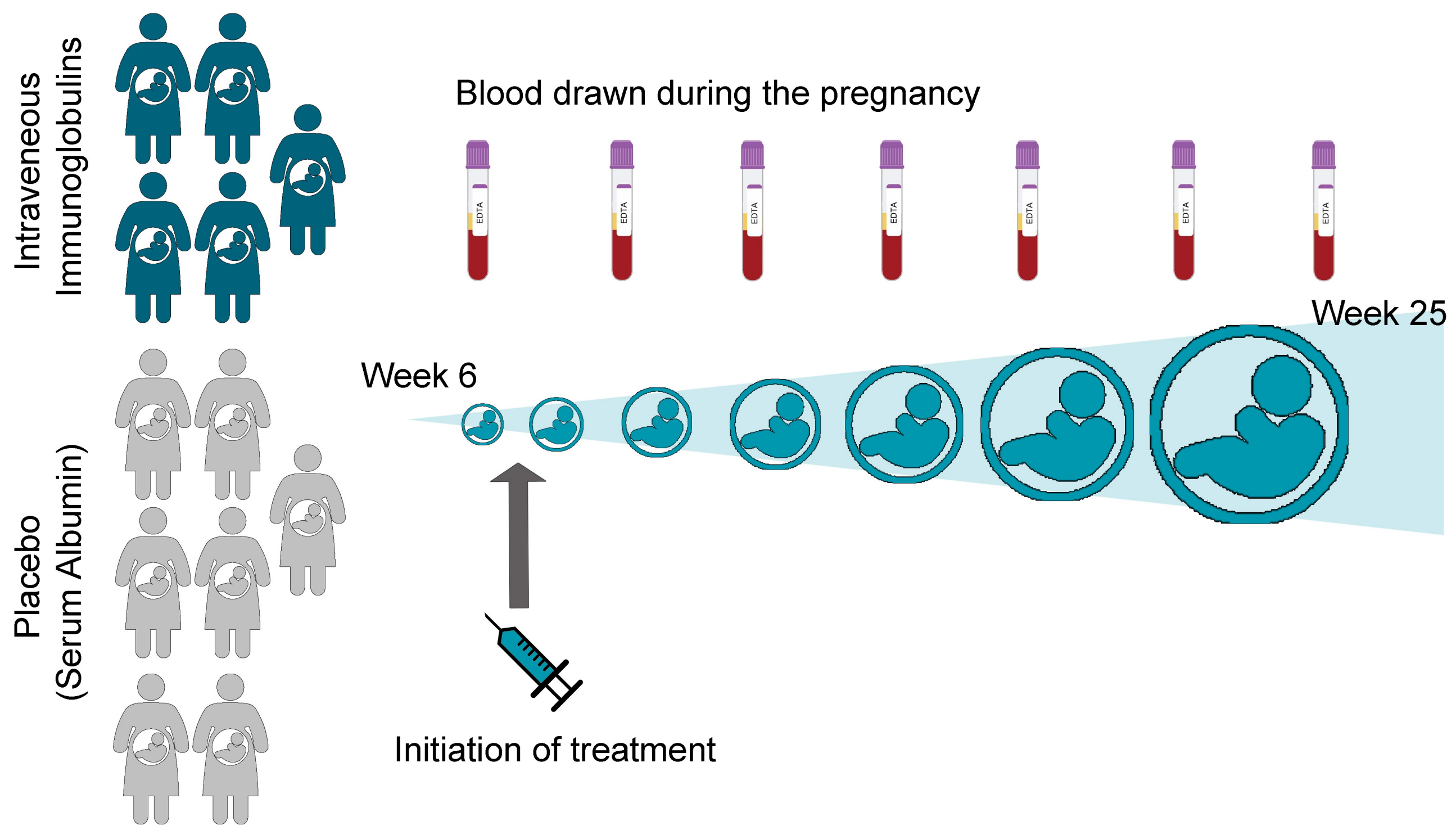
The highest increase were seen in sEVs carrying Placental Alkaline Phosphatase (PLAP) indicating that the newly produced sEVs originate from placenta. The level of sEVs positive for the two G-couple protein receptors Cholinergic Receptor Muscarinic 4 (CHRM4) and  $\beta$ -2 Adrenergic Receptor (ADRB2) showed the same increasing tendencies and it could be speculated, that the placenta had been activated by the treatment with Ivlg to produce more of these receptors.

This pilot study indicate that the level of sEVs in plasma are highly affected by treatment with Ivlg, but a larger cohort is needed to verify these observations.



## Study Design

Twelve women from the trial were included in this study, where 5 of the women were given treatment with Ivlg. The effect on plasma sEV phenotypes and levels were investigated during the pregnancy using the protein microarray based EV Array analysis platform (Baek *et al.*, 2017, Methods Mol Biol). In total 34 antibodies against surface-markers of interest were included.

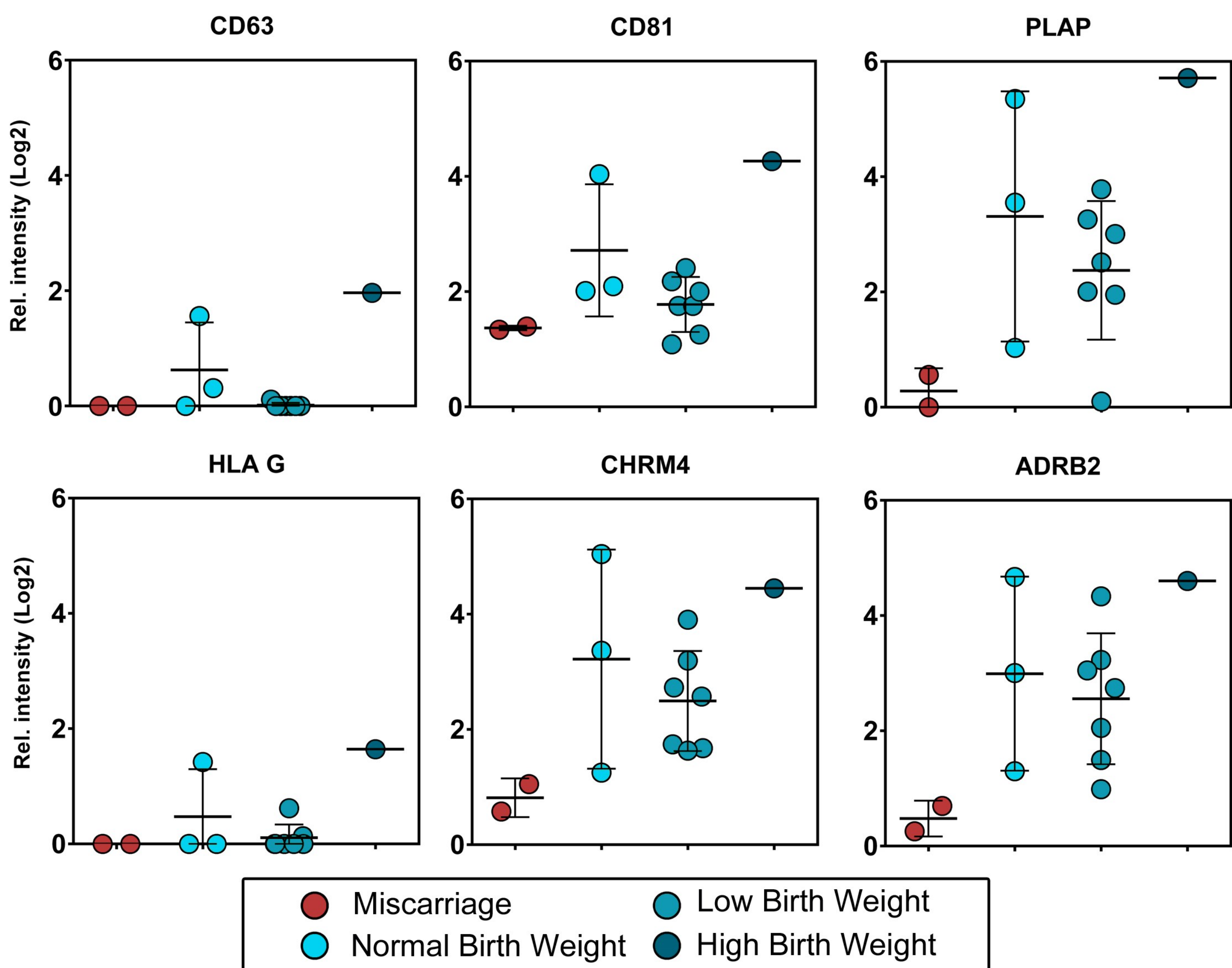


## Pregnancy Outcome

To answer, if it is possible to predict the pregnancy outcome early in the pregnancy the level of sEVs were compared using data from the first drawn blood sample. The two women who suffered from spontaneous miscarriage had the lowest amount of sEVs, which were seen for all of the EV surface molecules that were analyzed.

The women who gave birth showed already early in the pregnancy higher levels of sEVs carrying CD81, PLAP, HLA G, CHRM4 and ADRB2. Additionally, it seems that a high birth weight (above 4500 g) provides the highest levels of sEVs.

A larger cohort/study is needed for increasing the statistical power. However, the tendencies are notably towards that the birth outcome can be predicted from the sEVs present in plasma early in the pregnancy. Hence, that it can be a signal to initiate a treatment to prevent spontaneous miscarriage.



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